VERSION WITH MARKINGS TO SHOW AMENDMENTS MADE

Amendments to specification:

The paragraph at page 11, lines 18-21, of the specification is amended as follows.

Phospholipids were also tested as enhancers. It was found that a single-chain phospholipid ([lysophospatidylcholine] lysophosphatidylcholine) was an effective enhancer, while [two] one double-chain [phospholipids] phospholipid ([dioctanoylphosphatidylcholine and] didecanoylphosphatidylcholine) [were] was not. This may be explained by the fact that the double-chain [phospholipids are] phospholipid is much less soluble in water than [their] its single-chain [counterparts] counterpart; however, it is reasonable to expect that double-chain phospholipids of shorter chain length, having greater water solubility than their longer chain counterparts, will be of use as enhancers in the present invention so that both single- and double-chain phospholipids may be used.

Amendments to claims, other than cancellations and additions:

1. (Amended) A propellant-free composition[,] consisting [essentially] of (A) a polypeptide, (B) one or more surfactant compounds which (i) have a consistency that permits them to be processed into primary particles having a diameter less than 10 microns, and (ii) enhance the systemic absorption of said polypeptide in the lower respiratory tract of a patient, and (C) optionally one or more non-hygroscopic additives, said composition being in the form of a dry powder suitable for inhalation from a dry powder inhaler device, wherein at least 50% of the total mass of (A) and (B) consists of primary particles having a diameter less than or equal to about 10 microns, and wherein each of the one or more surfactant compounds is selected from the group consisting of a salt of a fatty acid, bile salt or derivative thereof, single-chain phospholipid, double-chain phospholipid in which each chain of the double-chain phospholipid is eight or fewer carbon atoms in length, alkyl glycoside, cyclodextrin or derivative thereof, salt of a

glycyrrhizine acid, salt of a saponin glycoside, salt of an acyl carnitine, and sodium salicylate.

2. (Amended) A composition as claimed in claim 1, including said one or more non-hygroscopic additives, said one or more non-hygroscopic additives comprising a carrier[, which] that comprises either

(a) particles having a diameter of less than about 10 microns, such that at least 50% of said composition consists of primary particles having a diameter of less than about 10 microns; or

(b) coarse particles having a diameter of at least 20 microns, such that an ordered mixture is formed between (i) the carrier and (ii) the polypeptide of (A) and the one or more [surfactants] surfactant compounds of (B).

12. (Amended) The composition of claim 1, wherein at least one of said one or more surfactant compounds is a bile salt[, a bile salt] or derivative thereof, an alkyl glycoside, a cyclodextrin or derivative thereof, or a phospholipid.

13. (Amended) The composition of claim 1, wherein at least one of said one or more surfactant compounds is a salt of a fatty acid.

16. (Amended) The composition of claim 1, wherein at least one of said one or more surfactant compounds is sodium caprate.

31. (Amended) The composition of claim 1, wherein at least one of said one or more [surfactants] compounds is a bile salt or derivative thereof.

REMARKS

The paragraph at page 11, lines 18-31, of the specification has been amended to correct a misspelling of "lysophosphatidylcholine" and to reword a statement that incorrectly implied that dioctanoylphosphatidylcholine did not enhance absorption of insulin in the lower respiratory tract. As shown at page 22, Table I of the specification, dioctanoylphosphatidylcholine did indeed enhance absorption, though to a lesser degree than other enhancers. The amendment thus corrects an inadvertent discrepancy between the data in Table I and the discussion of these data at page 11, lines 18-31.

Claims 1-10, 12-16, 21, 22, 26-32, 50-97, and 101-118 are now pending, new claims 102-118 having been added by the above amendments. Claim 1 has been amended to (1) specify that the claimed composition is "propellant-free," (2) change the transitional phrase from "consisting essentially of" to "consisting of," and (3) require that each of the one or more surfactant compounds be selected from a list of compound categories. Propellant-free compositions are supported by page 3, lines 9-16, of Swedish Patent Application No. 9302198-8, which describes insulin/enhancer formulations free of propellant, for use with dry powder inhalers.[1] The compound categories recited in claim 1 are supported by page 10, line 21, through page 12, line 13, of the present specification. In addition, double-chain phospholipids in which each chain of the phospholipid is eight carbon atoms in length or less are described at page 22, Table I of the specification, which shows that dioctanoyl-phosphatidylcholine enhanced absorption of insulin in the lower respiratory tract, but didecanoylphosphatidylcholine did not. Further support is found at page 11, lines 26-31, where the specification discloses that phospholipids with shorter chain lengths (and thus higher water solubility) than the one (didecanoylphosphatidylcholine) that Table I shows did not work "will be of use as enhancers." Claims 1, 2, 12, 13, 16, and 31 have been amended to clarify the claim language and to ensure that proper antecedent basis is provided for the claim terms.

Claims 1-10, 12-16, 31, and 101 essentially have been rewritten as new claims 102-118, except that new independent claim 102 (1) does not specify the optional inclusion of one or more

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[1]The present application claims priority from this Swedish application through USSN 08/265,237, the earliest U.S. application from which the present application claims priority. A certified copy of the Swedish application (in English) was submitted in parent USSN 08/265,237.

non-hygroscopic additives, (2) uses the transitional term "comprising" instead of "consisting of," and (3) requires that the dry powder be suitable for inhalation into the lower respiratory tract. These limitations are supported throughout the specification and by the claims as originally filed.

No new matter has been added by any of the above amendments.

Claims 2, 21, 22, 26-30, 32, and 50-97 have been withdrawn from consideration by the examiner because these claims are directed to unelected restriction groups. Applicants intend to rejoin one or more of these unelected restriction groups upon the examiner's determination that the claims under consideration are allowable, in accordance with the procedure set forth by the Examiner in his Restriction Requirement mailed December 30, 1999.

Rejections under 35 U.S.C. § 102

I

Claims 1, 3-10, 12, and 101 are rejected under § 102(e) as anticipated by Illum, U.S. Patent No. 5,707,644. Claims 3-10, 12, and 101 directly or indirectly depend from claim 1. Applicants have overcome this rejection by changing the transitional phrase "consisting essentially of" to "consisting of," thereby ensuring exclusion of any composition described in Illum.

The Illum patent describes microspheres which can be less than 10 μm (col. 2, lines 23-26) and which are formed from a gellable material, e.g., starch (col. 3, lines 26-30); a drug such as insulin (col. 7, lines 26-27); and optionally an absorption enhancer, e.g., bile salts (col. 6, line 43, to col. 7, line 11). Claim 1 excludes Illum's compositions. As noted above, Illum describes microspheres formed of (A) starch, (B) a polypeptide, and optionally (C) an enhancer. Therefore, Illum describes **AB** and **ABC**. In contrast, claim 1 recites a composition containing (B) a polypeptide, (C) one or more enhancers (i.e., surfactant enhancers), and (D) optionally one or more non-hygroscopic additives.[2] Therefore, claim 1 covers **BC** and **BCD**. Since there is no overlap between Illum's microspheres and the composition of claim 1, Illum does not anticipate the claim. Consequently, claim 1 and all claims dependent thereon are distinguishable from Illum, and the rejection should be withdrawn.

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[2]Applicants note that Illum's starch cannot be considered a "non-hygroscopic additive" within the meaning of claim 1 because the very purpose of Illum's starch is to absorp water and gel upon contact with a mucosal surface (col. 3, lines 26-28). Thus, Illum's starch, by definition, is hygroscopic.

In regard to new independent claim 102, it is noted that Illum is specifically interested in delivery of compositions to the nasal mucosa (see, e.g., col. 2, lines 18-21). Indeed, the gelling material acts as a bioadhesive so that the microspheres readily stick to a wet surface (e.g., the nasal mucosa) upon contact, a property that is key to Illum's invention (col. 2, lines 18-21; col. 3, lines 26-28; and col. 6, lines 24-34).

Therefore, there is no reason to expect, based upon Illum's teachings, that Illum's powder, a substantial proportion of which is gelling material, would be "suitable for inhalation into the lower respiratory tract," as required in claim 102. As discussed immediately above, the gelling material is designed to stick to the lining of the nose. Introducing such a sticky gel into the narrow airways and alveoli of the respiratory tract (where it is believed absorption of a polypeptide takes place, in accordance with the present invention) could interfere with normal gas exchange in the lungs and/or breathing. Thus, claim 102 and claims dependent thereon are distinguishable from Illum.

II

Claims 1, 3-10, 12, and 101 are rejected under § 102(b) as anticipated by Durrani, WO 91/16882. Claims 3-10, 12, and 101 directly or indirectly depend from claim 1. Applicants have overcome this rejection by requiring in claim 1 that each of the surfactant compounds be selected from specific compound categories, none of which includes Durrani's phospholipids. The phospholipids used for production of Durrani's liposomes are invariably double-chain phospholipids in which each chain of the phospholipid is at least 12 carbon atoms in length (see, e.g., page 8, Table 1). In contrast, amended claim 1 requires that the only double-chain phospholipid surfactant compounds that can be included in the claimed composition are those having chains of eight carbons or less. Since Durrani's phospholipids are excluded from the composition of claim 1, the reference does not anticipate claim 1 nor claims dependent thereon. This rejection should therefore be withdrawn. New claim 102 and claims dependent thereon are patentable over Durrani for the same reasons discussed immediately above.

III

Claims 1, 3-10, 12, and 101 are rejected under § 102(e) as anticipated by Patton, U.S. Patent No. 5,607,915. Claims 2-10, 12, and 101 directly or indirectly depend from claim 1. In accordance with the Examiner's suggestion, applicants have amended claim 1 to exclude

propellants from the claimed composition, thereby overcoming the rejection. New claim 102 also excludes propellants and is therefore patentable over Patton.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 3-10, 12-16, 31, and 101 are rejected as obvious over Patton in view of Clark (U.S. Patent No. 3,911,138), Poyton et al. (U.S. Patent No. 4,920,061), or Ecanow (U.S. Patent No. 4,914,084). Claims 3-10, 12-16, 31, and 101 depend directly or indirectly from claim 1. Applicants have overcome this rejection by implicitly excluding albumin as the recited surfactant compound in claim 1.

Patton describes dry powder formulations containing the polypeptide parathyroid hormone and human serum albumin as a bulking agent (col. 5, lines 46-48). The Examiner contends that, since the secondary references state that albumin is a surfactant, it is assumed that albumin functions as an enhancer compound in accordance with the claimed invention. Although applicants do not concede that Patton's unmodified human serum albumin can enhance absorption of a polypeptide in the lower respiratory tract, claim 1 has nevertheless been amended, for the sake of efficient prosecution to allowance, to require that the surfactant compound must be within recited compound groups, none of which includes albumin. Consequently, claim 1 excludes albumin as a possible surfactant compound, thereby rendering moot this rejection of claim 1 and claims dependent thereon.

It is noted that new claim 102 also excludes albumin as the recited surfactant compound. However, because the composition of claim 102 is defined using "comprising" as a transitional term, the composition can include albumin as, for example, a bulking agent. For such an embodiment of the claimed composition, it is noted that neither Patton nor any of the secondary references describes or suggests the inclusion of a surfactant compound selected from the categories recited in claim 102, in addition to the albumin already present in the composition. Consequently, claim 102 and claims dependent thereon are nonobvious over the cited references.

Examiner's Request for Information

The Examiner has asked applicants to point out the support for the "non-hygroscopic additives" recited in the claims. As discussed at page 7 of applicants' Response filed June 22, 1999, this term is supported at page 14, lines 12-32, of the specification. This portion of the

application discusses the inclusion of additives in dry powder compositions, such additives being non-hygroscopic (see page 14, lines 30-31).

CONCLUSION

Applicants submit that all of the claims under consideration are now in condition for allowance, which action is requested. If the claims under consideration are allowable, applicants would be willing to amend the pending claims directed to unelected inventions to also place those claims in condition for allowance. Applicants respectfully request that the Examiner contact the undersigned for that purpose.

Filed herewith is a check in payment of the excess claims fees required by the above amendments and Petition for Automatic Extension with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 1-12-01

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